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Biopharmaceutical evaluation of pseudoephedrine hydrochloride capsules containing different grades of sodium alginate

Peep Veski [a], Martti Marvola [b,*], Jaana Smal [b], Irene Heiskanen [b], Heidi Jürjenson [c]

[a] *Institute of Pharmacy, University of Tartu, Tartu, Estonia*
[b] *Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Helsinki, P.O. Box 15, FIN-00014 Helsinki, Finland*
[c] *Tartu University Women's Clinic, Tartu, Estonia*

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Abstract

In the study described here hard gelatin capsules containing pseudoephedrine hydrochloride and different grades of sodium alginate were prepared in order to obtain prolonged-release formulations. Evaluation was carried out by means of dissolution studies at three pH levels, 1.2, 4.4 and 7.2. Penetration of the dissolution medium into the capsule was followed by means of photographs. Bioavailabilities of the products were assessed in man. At pH 1.2 there was no difference between the formulations. At pH 7.2 release rates correlated with the viscosity grade of sodium alginate. The drug release mechanism could be explained on the basis of the photographs. The bioavailability tests confirmed that capsules containing high viscosity grades of alginate led to slow release formulations (t_{max} at 6.5 h) without any loss of amount of drug absorbed. It was concluded that the pseudoephedrine formulations, which are very simple to make, may be worth consideration in drug therapy.

Key words: Bioavailability; Hard gelatin capsule; Prolonged release; Pseudoephedrine; Sodium alginate

1. Introduction

Sodium alginates are polysaccharides. They are structurally linear copolymers that contain two types of sugar residue: D-mannuronate (M) and L-guluronate (G). They occur in alginate molecules in three types of sequence: poly-M, poly-G and poly-MG (McDowell, 1986). Sodium alginates are nontoxic. They are widely used in the food industry. They have also been extensively studied as additives to solid and liquid drug products for peroral administration (Stockwell et al., 1986; Zatz and Woodford, 1987; Fu Lu et al., 1991; Timmins et al., 1992; Ojantakanen et al., 1993).

Among the many manufacturers of sodium alginates Kelco Ltd is well known. It markets two series of alginates under the trade names Manugel™, which is rich in guluronic acid, and Manucol™, which is rich in mannuronic acid. We have studied the effects of 14 grades of sodium alginate on dissolution rates of ibuprofen from

* Corresponding author.

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hard gelatin capsules (Veski and Marvola, 1993). At pH 7.2, the dissolution rates of each formulation containing sodium alginate as a diluent followed zero-order kinetics and varied from 5.8 to 58.8% h^{-1}, depending mainly on the relative amounts and the viscosity grade of alginate used.

Results of bioavailability studies in man correlated well with in vitro data, and showed that it is possible using different grades of sodium alginate to prepare ibuprofen capsules from which absorption rates can be controlled over a fairly wide range, from slow release to extended-release formulations, without any decline in amount of drug absorbed (Veski et al., 1993). In this study the terms 'slow release' and 'extended-release' have been used to discriminate prolonged-release products into two subgroups as recommended by EC health authorities. Slow release products have higher t_{max} and lower C_{max} values than the corresponding immediate-release product, however, there is no difference in half-lives of the elimination phase. There is also a marked difference in the elimination half-life between extended-release and immediate-release products. It is longer for an extended-release preparation. The model drug used in these studies was only sparingly water soluble. With a drug that is highly soluble in water, it is possible that hard gelatin capsules containing sodium alginate as a diluent would behave differently. The effect of low pH on the drug release rate could also not be evaluated using formulations containing a weak acid as the model drug.

In the study reported here, the model drug was pseudoephedrine hydrochloride. It is highly water -soluble and its aqueous solubility does not depend markedly on pH level in the physiological range. Pseudoephedrine is a stereoisomer of ephedrine but has fewer central nervous system effects. It is used as a decongestant and is readily absorbed from the gastrointestinal tract. It is largely excreted unchanged in the urine, with an elimination half-life of 5–8 h (Kuntzman et al., 1971; Yacobi et al., 1980; Lin et al., 1985).

The primary aim of the study reported here was to study the effect of pH of the dissolution medium on the release rate of pseudoephedrine hydrochloride from hard gelatin capsule formulations containing four grades of sodium alginate. Secondarily, penetration of the dissolution medium into the capsule was studied and an attempt was made to discover the mechanism by which the formulation acts as a modified-release preparation. Finally, the bioavailabilities of the formulations in healthy volunteers were evaluated.

2. Materials and methods

2.1. Capsule formulations

Size 0 hard gelatin capsules (Posiloc™, Elanco) were used for all formulations. The amount of pseudoephedrine hydrochloride (Knoll AG) per capsule was 100 mg. Four grades of sodium alginate (Kelco Ltd) were used as diluent. The trade names and viscosities (at 25°C) of 1% (w/w) aqueous solutions of these sodium alginates were: Manugel DPB (500 mPa s), Manugel GHB (75 mPa s), Manucol DM (250 mPa s) and Manucol LD (9 mPa s). The particle size of all of the sodium alginates was < 355 μm as given by the manufacturer.

The amounts of drug needed were weighed in graduated cylinders and diluent added to produce sufficient material for 25 capsules (17 ml). Amounts of sodium alginate per capsule were: Manugel DPB 431 mg, Manugel GHB 489 mg, Manucol DM 513 mg and Manucol LD 513 mg. The powders were mixed manually, and capsules were filled using a Feton apparatus. The reference capsule in the bioavailability study contained 100 mg of pseudoephedrine hydrochloride without additive.

2.2. Drug dissolution

Dissolution of pseudoephedrine hydrochloride from capsules was determined using the USP rotating basket method. Solvents with three pH values were used, namely, (1) pH 1.2 (0.1 mol/l hydrochloric acid), (2) pH 4.4 (phosphate buffer containing 6.81 g of KH_2PO_4 in 1 l of water) and (3) pH 7.2 (phosphate buffer containing 6.81 g of KH_2PO_4 and 1.39 g of NaOH in 1 l of water). The volume of dissolution medium was 900 ml

and the temperature 37°C. The speed of rotation was 150 min^{-1}. Samples were taken manually. Drug concentrations were determined using the HPLC method described in section 2.5 (Dowse et al., 1983). The volume of sample administered to the injector was 10 μl. No extraction of samples was needed. Goodness of fit of dissolution curves to first-order and square-root-of-time equations was evaluated using Minsq™ software (Micromath).

2.3. Penetration of dissolution medium into capsules

The test was analogous to the ordinary dissolution test but the dissolution medium contained 0.1% fuchsin (E. Merck), which gave the solution a red colour. At predetermined times, capsules were removed from the dissolution apparatus and cut into two. Penetration of the coloured solution was evaluated by visual inspection and photography.

2.4. Bioavailability study

Two groups of eight healthy volunteers (four women and four men in both groups) participated in randomized crossover single-dose studies. These were carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly, 1975) as revised in Tokyo. The ages of the volunteers ranged from 19 to 24 years, and their weights from 45 to 84 kg. All were nonsmokers. None took any drug during the study or 1 week before it. 1 week prior to the study, participants underwent physical examination, routine laboratory tests and ECG examination. The study protocol had been approved by the Ethical Committee of the University of Tartu.

One capsule containing 100 mg of pseudoephedrine hydrochloride was administered with 200 ml of water following overnight fasting for at least 10 h. A standard lunch was provided 4 h after drug administration. The first group received reference capsules and capsules containing Manugel DPB, the second group capsules containing Manucols. The wash-out period between formulations was 1 week.

Blood samples of 10 ml were collected from a forearm vein into heparinized tubes just prior to drug administration, and 1, 2, 3, 4, 6, 8, 10, 12 and 24 h thereafter. Plasma was separated approx. 30 min after collection by centrifugation ($3000 \times g$ for 10 min), and frozen at -20°C until analyzed.

2.5. Plasma assay

Pseudoephedrine plasma concentrations were determined by high-performance liquid chromatography (HPLC), using a modified version of the method of Dowse et al. (1983). 1 ml of plasma, 50 μl of a saturated solution of sodium carbonate and 100 μl of 2 M sodium hydroxide solution were vortexed for 15 s. 4 ml of diethyl ether were added and the tube was vortexed for 1 min and centrifuged for 5 min. 2 ml of ether extract were transferred to a centrifuge tube containing 100 μl of 5% acetic acid. The mixture was vortexed for 1 min and centrifuged for 5 min. The ether layer was reduced and the water layer transferred to a clean tube, from which 50 μl were taken for determination of drug levels. Each plasma sample was analyzed in triplicate. Mean values were used.

The system was equipped with a Waters Model 501 piston pump, a Waters Model 717 Intelligent Sample Processor, a Waters Model 486 Turnable Absorbance Detector operating at 220 nm and a Waters Model 820 Maxima Workstation. Sample separation was carried out on a μBondapak C_{18} reverse-phase column (3.9×300 mm). The guard column used was a μBondapak C_{18}.

The mobile phase was prepared by mixing acetonitrile (200 ml) with a 0.005 M solution of sodium 1-heptanesulphonate in water (800 ml) and adding 2 ml of 1 M hydrochloric acid. The flow rate was 1.3 ml min^{-1}. All chemicals were analytical or HPLC grade.

The standard curve was found to be linear over the concentration range 50–1000 ng ml^{-1} and passed close to the origin. The linear coefficient of determination was 0.993 or better. Accuracy and precision of the method were investigated as recommended by Shah et al. (1992), by analyzing six plasma samples of pseudoephedrine

concentrations of 50 and 500 ng ml^{-1}. Mean values were 45.4 ng ml^{-1} (CV 18.3%) and 484 ng ml^{-1} (CV 2.7%). The limit of quantitation was estimated to be 50 ng ml^{-1}. No interfering peaks were observed in the plasma blanks.

2.6. Pharmacokinetic parameters

The pharmacokinetic parameters assessed using the Siphar™ program (Simed) were: maximum plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the concentration-time curve from time zero to infinity (AUC), elimination half-life ($t_{\frac{1}{2}}$) and mean residence time (MRT). C_{max} and t_{max} values were used as measured. AUC and MRT values were calculated according to the trapezoidal method, without logarithmic transformation. The ratio C_{max}/AUC was also calculated. Statistical analyses were carried out using Student's t-test or Student's paired t-test. Values of t_{max} were analyzed using the nonparametric tests of Wilcoxon and Mann-Whitney.

3. Results and discussion

3.1. Dissolution studies

When the hard gelatin capsule contained only 100 mg of pseudoephedrine hydrochloride, dissolution of the drug reached completion within 15 min, regardless of the pH of the dissolution medium. Fig. 1 shows the effect of pH on dissolution of pseudoephedrine hydrochloride from the four formulations that also contained sodium alginate. At pH 1.2, which should mimic in vivo conditions in the stomach, there were no differences between the four formulations. At higher pH values, the capsule containing the lowest viscosity grade alginate, Manucol LD, differed markedly from the others. The differences between the other three alginates were minimal, especially at pH 7.2.

When the capsules contained Manucol DM, Manugel GHB or Manugel DPB, the release rate of pseudoephedrine hydrochloride was highest at pH 1.2 and lowest at pH 4.4, except for Manugel DPB at pH 7.2. Capsules containing the lowest viscosity grade alginate (Manucol LD) differed markedly in their behaviour. Slowest drug release was achieved at pH 1.2 and the highest at pH 7.2.

In most cases, the release profiles of pseudoephedrine hydrochloride (Fig. 1) best fitted first-order kinetics. The only exceptions were Manucol LD capsules at pH 4.4 and 7.2, where the best model followed square-root-of-time kinetics. In this respect, the results in this study differ from our previous data with ibuprofen as model drug (Veski and Marvola, 1993). In our earlier study the only dissolution pH used was 7.2, due to the solubility of the drug. In that study the drug-release profile followed zero-order kinetics, irrespective of the grade of sodium alginate used in the capsules. The difference in kinetic profiles can be explained on the basis of the aqueous solubility of the drugs. Overall release rates for ibuprofen were lower than those obtained for pseudoephedrine hydrochloride. In addition, the release rate of ibuprofen was more readily controllable using different grades of sodium alginate.

The results reported here only partially correspond to those reported in the literature. Stockwell et al. (1986) reported that a cationic drug (chlorpheniramine maleate) had a slower release rate from alginate matrices than an anionic drug (sodium salicylate). In our study, an anionic drug (ibuprofen) was used as such, not as a water-soluble salt. In addition, unlike the matrix capsules of Stockwell et al., our capsule formulations did not contain calcium phosphate or sodium bicarbonate. These affect the gelation properties of alginate and the pH of the matrix. As far as in vitro results are concerned, the conclusion from our experience is that a simple capsule formulation, containing only the drug and sodium alginate, is better with drugs that are only sparingly soluble in water, e.g., weak acids, than with highly water-soluble drugs, e.g., hydrochloride salts of basic drugs.

Timmins et al. (1992) prepared sodium alginate matrix tablets containing verapamil hydrochloride. They found that the release rates were partially independent of the pH of the dissolution

medium. When matrices were prepared from sodium alginate rich in mannuronic acid (e.g., Manucol DMF), the dissolution pH (1.2 or 7.4) had no marked effect on dissolution rate. In contrast, if the alginate used was rich in guluronic acid (e.g., Manugel DMP), a reduction in pH led to a significantly higher release rate for verapamil hydrochloride. Our results indicate pH-dependent dissolution of pseudoephedrine hydrochloride for all four grades of sodium alginate studied. With Manucol DM, Manugel GHB and Manugel DPB, the dissolution rate was highest at pH 1.2. With Manucol LD it was lowest at the same pH.

3.2. Penetration studies

In order to obtain more information on the formulation, a dye (fuchsin) was added to dissolution media. At various times a capsule was removed, cut into two, and photographed (Fig. 2). The pH of the solution was 1.2 and the capsules contained Manugel DPB as additive.

At 30 min three layers were visible. The outer layer was tight and fairly hard. The second layer was gelatinous and smooth. The intensity of red colour in this layer was stronger than that in the outer layer. The core of the capsule was dry. At 1–3 h all three layers were clearly evident. The thickness of the outer layer increased more rapidly than that of the second layer. The photograph at 4 h was the last in which dry powder was visible in the core. At 6 h the gelatinous part had almost totally disappeared. The total volume of the formulation did not increase, i.e., there was no marked swelling of sodium alginate.

It is obvious that hydrochloric acid reacts with sodium alginate, and that an outer layer is formed when colloidal alginic acid precipitates. It is possible that the gelatin shell also plays a role in the commencement of formation of an outer layer. When dissolution medium penetrates the capsule, hydrogen ions are exchanged for sodium ions, and the dissolution medium declines in acidity. The second gelatinous layer is therefore formed when only slightly acidic or almost neutral solution moistens the sodium alginate. This explains why there was no difference in the dissolution curves between formulations at pH 1.2

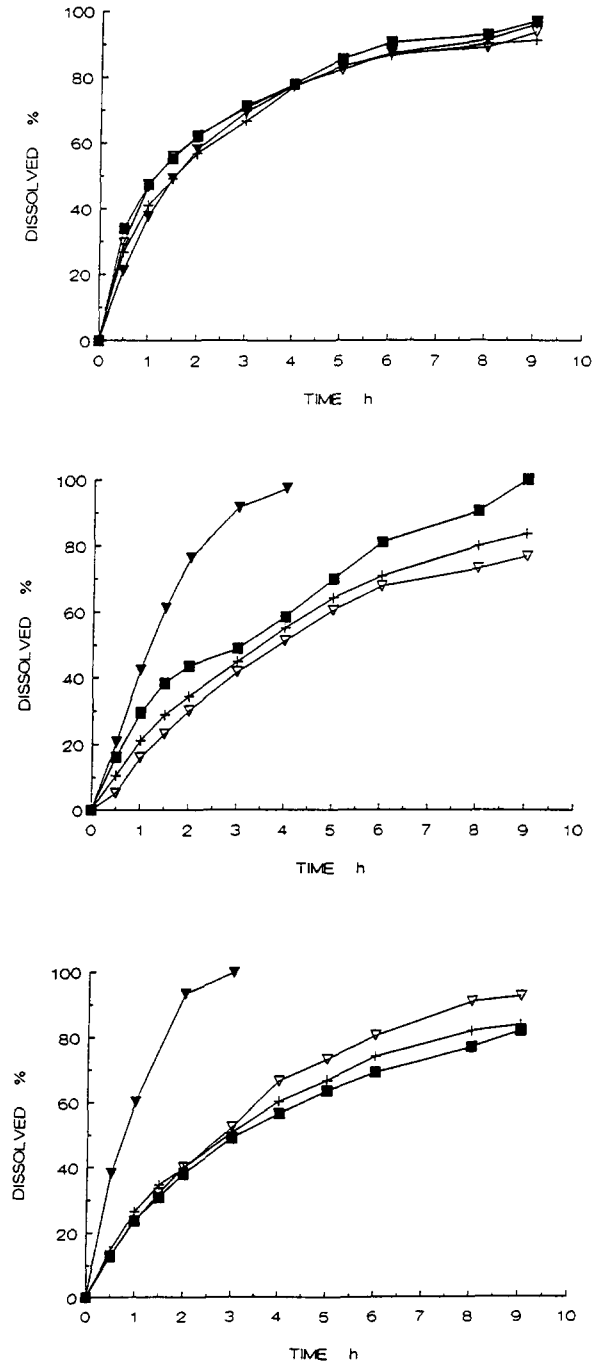

Fig. 1. Dissolution of pseudoephedrine hydrochloride from hard gelatin capsules containing different grades of sodium alginate as diluent: (▼) Manucol LD, (▽) Manucol DM, (+) Manugel GHB, (■) Manugel DPB. pH of dissolution medium was 1.2 (top), 4.4 (middle) or 7.2 (bottom); means of six parallel tests.

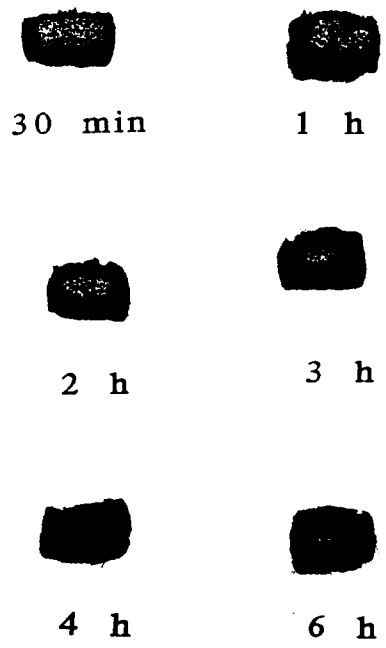

Fig. 2. Photographs showing penetration of the coloured dissolution medium into pseudoephedrine hydrochloride capsules containing Manugel DPB as diluent. The figures show the times when the capsules were removed from the dissolution equipment.

(Fig. 1). In all formulations, alginic acid precipitated and formed the tight outer layer that acted as a rate-limiting layer in relation to diffusion of pseudoephedrine hydrochloride.

As the pH of the dissolution medium increased (4.4 or 7.2) no precipitation of alginic acid took place. The outer layer consisted only of sodium alginate gel and its tightness depended on the viscosity grade and chemical nature of the sodium alginate used.

The question now arises as to why Manucol LD behaved differently from the other three grades of sodium alginate. The viscosity grade of Manucol LD is very low (9 mPa s). The gel formed from it at pH 4.4 or 7.2 creates only a very weak barrier to diffusion of the drug. When a dissolution test is carried out at pH 1.2, colloidal alginic acid creates a tight outer layer that forms a better barrier than the low-viscosity sodium alginate gels formed at the higher pH values.

3.3. Bioavailability studies

Fig. 3 and 4 show mean curves for the two bioavailability studies. The corresponding individual curves are shown in Fig. 5. Table 1 lists the calculated pharmacokinetic parameters for each formulation. Results of statistical analyses are given in Table 2. There were no statistically significant ($p > 0.05$) differences in the extent of bioavailability (AUC values) between the four formulations. When the capsules containing

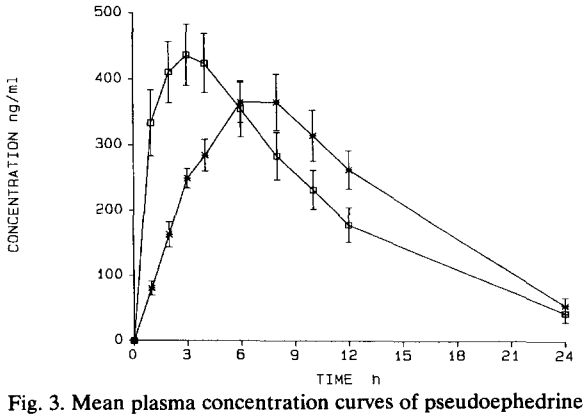

Fig. 3. Mean plasma concentration curves of pseudoephedrine after administration of 100 mg of pseudoephedrine hydrochloride in capsules containing the drug alone (□) or in capsules containing Manugel DPB as diluent (*); means ± S.E., $n = 8$.

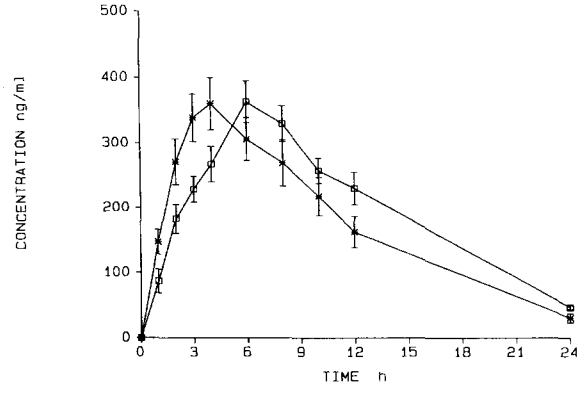

Fig. 4. Mean plasma concentration curves of pseudoephedrine after administration of 100 mg of pseudoephedrine hydrochloride in capsules containing Manucol LD (*) or Manucol DM (□) as diluent; means ± S.E., $n = 8$.

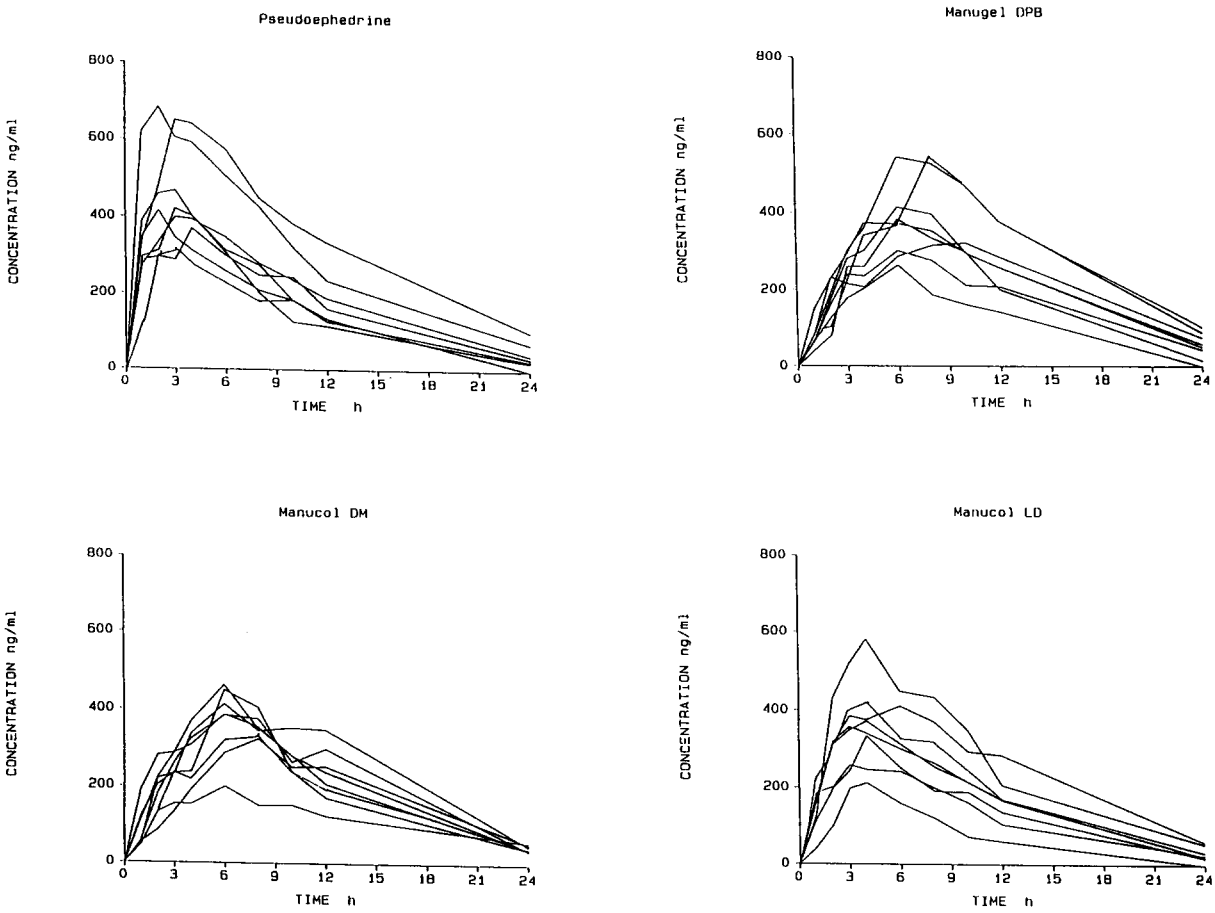

Fig. 5. Individual plasma concentrations of pseudoephedrine after administration of 100 mg of pseudoephedrine hydrochloride in different capsule formulations. Formulations: (A) capsule containing drug alone, (B) capsule containing Manugel DPB as diluent, (C) capsule containing Manucol DM as diluent, and (D) capsule containing Manucol LD as diluent.

sodium alginate were compared with the reference capsule, significant differences were found in the pharmacokinetic parameters describing the rate of bioavailability (t_{max}, MRT and C_{max}/AUC).

When the lowest viscosity grade alginate

Table 1
Pharmacokinetic parameters of pseudoephedrine in hard gelatin capsules containing different grades of sodium alginate as diluent

Parameter	Reference	Diluent		
		Manugel DPB	Manucol DM	Manucol LD
AUC (ng ml^{-1} h)	5465 ± 2082	5742 ± 1668	5121 ± 810	4428 ± 1607
C_{max} (ng ml^{-1})	466 ± 131	392 ± 104	369 ± 85	368 ± 112
t_{max} (h)	2.88 ± 0.64	6.50 ± 1.77	6.50 ± 0.93	4.00 ± 0.93
$t_{1/2}$ (h)	5.98 ± 0.94	6.04 ± 1.11	6.31 ± 1.83	4.81 ± 0.57
MRT (h)	9.56 ± 1.27	11.8 ± 1.41	11.7 ± 2.45	9.18 ± 0.79
C_{max}/AUC (h^{-1})	0.088 ± 0.013	0.069 ± 0.010	0.072 ± 0.011	0.087 ± 0.016

Reference capsules contained only the drug. Single peroral dose: 100 mg of pseudoephedrine hydrochloride (means ± S.D., $n = 8$).

Table 2
Statistical analysis of calculated pharmacokinetic parameters for pseudoephedrine capsules containing different grades of sodium alginate as diluent

Parameter	Diluent		
	Manugel DPB	Manucol DM	Manucol LD
AUC	NS	NS	NS
C_{max}	NS	NS	NS
t_{max}	[b]	[b]	[a]
$t_{\frac{1}{2}}$	NS	NS	NS
MRT	[a]	[a]	NS
C_{max}/AUC	[a]	[a]	NS

Reference values are parameters obtained for capsules containing the drug alone. Statistical methods: Student's paired t-test for Manugel DPB, Student's unpaired t-test for Manucol DM and Manucol LD.
[a] = $p < 0.05$; [b] = $p < 0.01$; NS, not significant.

(Manucol LD) was used, prolongation of the absorption phase was relative low, e.g., a change in mean t_{max} value from 2.88 h (reference) to 4.00 h. There were no significant differences in MRT and C_{max}/AUC values (Table 1). When Manucol DM or Manugel DPB was used, absorption of pseudoephedrine was more obviously retarded: t_{max} for both formulations was 6.5 h. MRT and C_{max}/AUC values also differed statistically significantly from those for the reference capsule (Table 2). As far as apparent elimination half-lives ($t_{\frac{1}{2}}$) were concerned, there were no differences between the reference capsule and those containing sodium alginates. The conclusion from the results of in vivo studies is therefore that formulations containing Manucol DM or Manugel DPB can be classified as slow release preparations.

When the bioavailabilities of similar capsules containing ibuprofen instead of pseudoephedrine hydrochloride were investigated the conclusion was that formulations containing Manucol DM or Manugel GHB could be classified as a slow release preparation whereas the formulation containing Manugel DPB was an extended-release preparation (Veski and Marvola, 1993). The results of in vivo studies therefore confirmed the conclusion from results of in vitro tests that capsule formulations containing sodium alginate are better in relation to drugs that are sparingly soluble in water than in relation to highly water-soluble drugs.

The interindividual variation evident in Fig. 5 is normal for such modified-release formulations, especially if variation in weights of volunteers (45–84 kg) are taken into account. AUC values with slow release formulations in the study reported here (5742 and 5121 ng ml^{-1} h) are greater than the corresponding value for a commercial modified-release product (4483 ng ml^{-1} h), although the pseudoephedrine hydrochloride dose was lower: 100 vs 120 mg (Wecker et al., 1987). In addition, t_{max} occurred at 6.5 h in the study reported here. With the commercial preparation t_{max} occurred at 4.5 h. The pseudoephedrine formulations described here could therefore be worth considering in clinical situations.

3.4. Comparison of in vitro and in vivo results

Results of in vitro studies in acid environments, e.g., at pH 1.2, are often thought to allow optimum prediction of the in vivo fate of a drug product. In the study reported here, there were no differences between formulations at pH 1.2 (Fig. 1). In vivo, however, differences between formulations were evident (Fig. 3 and 4; Table 1).

It is possible that the capsules remained for 0.5–2 h in the stomachs of volunteers. During this time, an outer layer consisting of precipitated alginic acid is formed. A similar layer is also seen in vitro studies (Fig. 2). The alginic acid layer, which is not hydrophilic, does not favour adherence of the formulation to the gastric mucosa for a long time. Under fasting conditions, movements of the migrating myoelectric complex ('housekeeper' wave), appearing approximately every second hour (Minami and McCallum, 1984), therefore sweep the capsule into the small intestine. The solution subsequently penetrating into the capsule is no longer acid. The rest of the sodium alginate in the core forms a gel. Its tightness depends on the viscosity grade of the polymer. This is why the in vivo absorption rate correlates with the viscosity grade of sodium alginate although no differences were seen in dissolution studies at pH 1.2.

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